Difluorocarbene Generation from $TMSCF_3$: Kinetics and Mechanism of NaI-Mediated, and Si-Induced, Anionic Chain Reactions

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ABSTRACT: The mechanism of CF_2-transfer from $TMSCF_3$ (**1**), mediated by TBAT (2–12 mol%) or by NaI (5–20 mol%), has been investigated by in situ / stopped-flow ^{19}F NMR spectroscopic analysis of the kinetics of alkene difluorocyclopropanation, and competing TFE / *c*-C_3F_6 / homologous perfluoroanion generation, $^{13}C/^{2}H$ KIEs, LFERs, CF_2-transfer efficiency and selectivity, the effect of inhibitors, and density functional theory (DFT) calculations. The reactions evolve with profoundly different kinetics, undergoing auto-inhibition (TBAT) or stochastic auto-acceleration (NaI), and co-generating perfluoroalkene side products. An overarching mechanism involving direct and indirect fluoride transfer from a CF_3-anionoid to $TMSCF_3$ (**1**) has been elucidated. It allows rationalization of why the NaI-mediated process is more effective for less-reactive alkenes and alkynes, why a large excess of $TMSCF_3$ (**1**) is required in all cases, and why slow-addition protocols can be of benefit. Issues relating to exothermicity, toxicity, and scale-up are also noted.

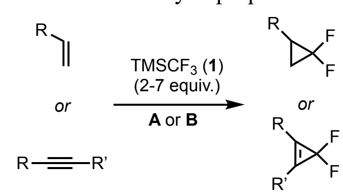
INTRODUCTION

The unique properties of cyclopropanes leads to useful effects on their fluorination,[1] with the application of difluorocyclopropanes being especially prominent.[1-2] The latter are most commonly prepared by alkene-difluorocyclopropanation,[1-3] nominally via in situ capture of singlet CF_2,[4] and over the last 50 years, a very broad range of reagents have been developed for this process.[5-10] However, many of these reagents have limitations, inter alia, toxicity, the use of strong bases, or the need for high-temperatures. The latter aspect is of critical importance for alkynes, where the primary difluorocyclopropene product can undergo further difluorocyclopropanation and other reactions.[11] Thus, there has been much interest in the development of new reagents,[9] and major advances have been independently made by Dilman and co-workers,[3c,9fgh,t] and by Prakash and Hu and co-workers,[8c,10] in the use of $TMSCF_2X$ species (X = F, Cl, Br, I) for CF_2-transfer under mild conditions.

The Prakash-Hu difluorocyclopropanation, Scheme 1, employing commercially-available $TMSCF_3$ (**1**), and in particular the use of NaI in THF (conditions B),[10] is now widely-applied,[12] e.g. in the extensive studies of Grygorenko and co-workers,[12i,m,n,p] and Mykhailiuk and co-workers,[12h,l] and in a difluorocyclopropanation flow-reactor developed by Charette and co-workers.[12b] Conditions analogous to B, Scheme 1, but omitting the alkene, have also been applied by Hu and co-workers for the preparation of tetrafluoroethylene (TFE), and its reactive dissolution in a second vessel.[13h] This allows a range of -CF_2CF_2- containing species to be generated from $TMSCF_3$ (**1**), without direct, and potentially hazardous, manipulation of TFE.[14]

Thus, $TMSCF_3$ (**1**), a reagent that has been employed for over 30 years for the nucleophilic transfer of CF_3,[15] has recently undergone a major renaissance, as a 'CF_2-surrogate'.[10,12,13] There are considerable similarities between the conditions employed for CF_3-transfer from **1** to electrophiles,[15c] versus those employed for CF_2-transfer to alkenes/ynes.[10,12] However, a prominent disparity is the large excess of $TMSCF_3$ (2-7 equivalents) used for CF_2-transfer. Indeed, this issue has prompted Grygorenko and co-workers to develop a 'slow-addition protocol' allowing substantial improvement in the efficiency and substrate diversity of the difluorocyclopropanation process.[12m,p]

Scheme 1. Prakash-Hu difluorocyclopropanation.[a10,12]



[a.] TBAT = $[Bu_4N]^+[Ph_3SiF_2]^-$. [b.] –50 °C to RT. [c.] Alkyne at 110 °C.

Despite the major synthetic developments outlined above, the kinetic and mechanistic details of CF_2-transfer from $TMSCF_3$ (**1**), not just to alkenes and alkynes,[10,12] but to a wide range of other species,[13] remains largely unexplored.[3,12m]

RESULTS AND DISCUSSION

We recently confirmed that CF_3-transfer from $TMSCF_3$ (**1**) to ketones and aldehydes involves liberation of a transient CF_3-anionoid, rather than direct CF_3-transfer from a trifluoromethyl siliconate $[Me_3Si(X)CF_3]^-$ (**2**$_X$; X = alkoxy or CF_3).[16-18] Herein we describe a detailed study of the mechanism of CF_2-transfer from $TMSCF_3$ (**1**) to alkenes and alkynes, under the Prakash-Hu difluorocyclopropanation conditions, Scheme 1.[10] Extensive in situ ^{19}F NMR spectroscopic investigation has allowed us to analyse the reaction kinetics, the selectivity, and the side reactions that lead to the requirement for a large excess of the $TMSCF_3$ (**1**) reagent. As with our study on CF_3-transfer,[16] concurrent analysis of numerous intermediates and processes using density functional theory (DFT) has been crucial in informing and constraining the investigation.

1. Prior Studies. Common to most proposals for the mechanism of the Prakash-Hu difluorocyclopropanation[10,12] is the assumption that i) the process involves generation of free CF_2 from **1**, which then adds to the alkene,[10,12] and ii) that the CF_2 arises from direct loss of fluoride (k_α) from a transient CF_3-anionoid,[19,20] Mechanisms I, II, Scheme 2. In the absence of alkene, the CF_2 is suggested to spontaneously dimerize to give TFE.[13h] Fluoride ions have been proposed[10,13b,f] to have two distinct roles in these reactions. Nonmetallic fluorides, such as $[Bu_4N]^+[Ph_3SiF_2]^-$ ('TBAT'), are suggested[10,13b] to initiate a fluoride-mediated chain reaction (Mechanism I). Conversely, metal iodides, such as NaI, are suggested[10,13b,f] to displace a CF_3-anionoid from $TMSCF_3$ (**1**), with the TMSI coproduct trapping the nascent fluoride from the CF_2 generation (Mechanism II), thus inhibiting Mechanism I. Intriguingly, the possibility of an α-elimination at silicon[21] (k_αSi), Mechanism III, X = CF_3, F, I) has not been discussed, despite the *indirect* role of siliconates $[Me_3Si(X)CF_3]^-$ ($\mathbf{2_X}$)[17] in CF_3-anionoid transfer.[16-18]

Scheme 2. Mechanisms I and II, previously proposed[10,13b,f] for CF_2-generation from $TMSCF_3$ (**1**), and mechanism III involving α-elimination in a siliconate ($\mathbf{2_X}$, X = CF_3, F, I). See text for full discussion.

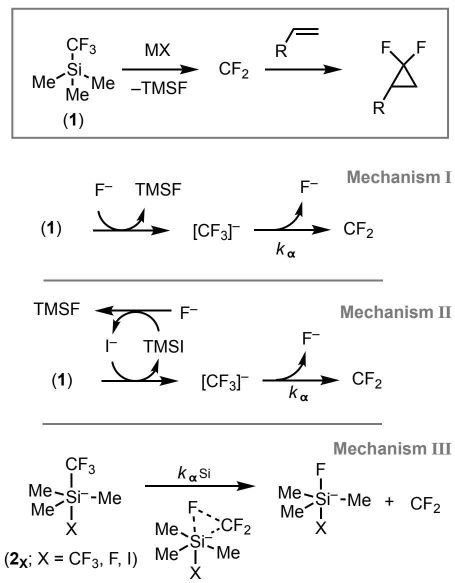


Table 1. Difluorocyclopropanation of alkenes **3i**, and *E*/*Z*-**4** and alkyne **5** in THF. The k_{rel}[a] and ρ^{+b} values are independent of the method: **1** + TBAT (conditions A); **1** + NaI (conditions B),[10] or thermalization of $Ph_3PCF_2CO_2$.[22]

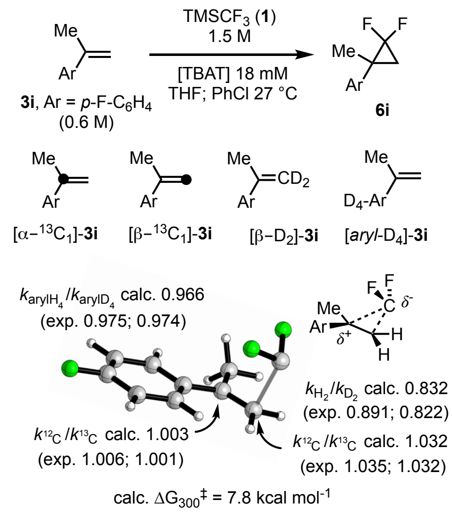
	Alkene/yne	Product		$k_{rel.}$ (21 °C)[a]	$k_{rel.}$ (65 °C)[a]
3i	Me, p-F-C_6H_4	F, F, Me, p-F-C_6H_4	(±)-**6i**	1.00	1.00
E-**4**	Me, Ph	F, F, Ph, Me	*trans*-(±)-**7**	0.05	0.08
Z-**4**	Ph, Me	F, F, Ph, Me	*cis*-(±)-**7**	0.01	0.02
5	Ph—≡—Me	F, F, Ph, Me	**8**	0.17	0.22
				ρ^+(21 °C)	ρ^+(65 °C)
3i-vii	Me, p-X-C_6H_4	F, F, Me, p-X-C_6H_4	(±)-**6i-vii**	–0.64 (–0.74)[b]	–0.61 (–0.63)[b]

X = F(**i**); H (**ii**); Ph (**iii**); Me (**iv**) MeO (**v**); CF_3 (**vi**); Br (**vii**)

[a]Relative rates (k_{rel}) are for competitive first-order CF_2 capture by the alkene/yne, not to overall rates of reaction. [b]Values in parenthesis by DFT.[26] See sections S3.7, S3.8 and S6.2 in the SI.

2. Singlet CF_2 as the Reactive Intermediate. We began by studying the reaction of $TMSCF_3$ (**1**) with alkenes **3i**, and *E*/*Z*-**4** and alkyne **5**, Table 1. All underwent difluorocyclopropanation, to varying degrees of conversion, in the presence of $TMSCF_3$ (**1**, 1.5 M) and 1-5 mol % TBAT, or NaI. Reactions of *E*/*Z*-**4** proceeded stereospecifically, and with >98 % retention. The difluorocyclopropene **8**, generated in low yield (12%) from alkyne **5**, under the TBAT-mediated conditions, underwent partial decomposition to unidentified products. In contrast, **8** was quantitatively-generated, and stable, under NaI-mediated conditions, see section S3.3 in the SI. The same difluorocyclopropane products (**6**, **7**) were obtained from **3i** and *E*/*Z*-**4** on thermalization with the zwitterionic CF_2-source $Ph_3PCF_2CO_2$.[22] The relative reactivities (k_{rel}) of alkenes **3i**, *E*-**4**, and *Z*-**4**, and the LFER correlation for α-methylstyrenes (**3i-vii**, ρ^+ = –0.6),[23] were independent of the reagent (**1** / $Ph_3PCF_2CO_2$), and initiator (TBAT / NaI), Table 1,[24] within experimental error.

Scheme 3. Experimental[a] and calculated[b] KIEs for rapid addition of transient singlet CF_2 to **3i**, at 300 K.[25]



[a]Experimental (exp.) values in THF; and in PhCl, as solvent.[25] [b]Calculated (calc.) values by DFT, at the M06/6-31+G* level in Gaussian09 employing IEF-PCM single points to account for solvation, and goodvibes, kinisot and PyQuiver to compute free energy corrections and KIEs, see sections S1.6 and S6.2 in the SI.[26]

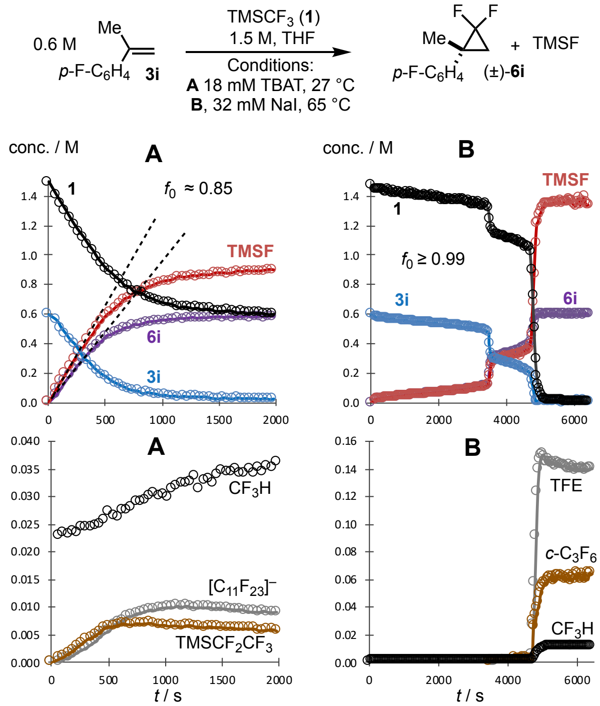
Kinetic isotope effects for the reaction of p-F-α-methylstyrene **3i** with $TMSCF_3$ (**1**) initiated by TBAT were obtained by a series of competitions of ^{13}C- and ^2H-labelled α-methylstyrenes **3i** against *aryl*-D_4-**3i**, monitored by ^{19}F NMR spectroscopy (*aryl*-$\Delta\delta_F$ = 0.5 ppm).[25] The resulting primary and secondary kinetic isotope effects, Scheme 3, were consistent with those predicted by DFT calculations,[16,26] for the rapid addition of singlet CF_2 to **3i**, see section S6.2 in the SI.[4,27] The concerted asynchronous cycloaddition of CF_2 is also consistent with the LFER correlation (ρ^+ –0.64, Table 1), and with *E*-**4** being about 5-fold more reactive than *Z*-**4**.

Overall, the preliminary studies above strongly support the conclusion that $TMSCF_3$ (**1**) functions as an *indirect*[28] source of free singlet CF_2.[4] However, as is evident from Figure 1, the two sets of conditions, Scheme 1,[10] evolve with profoundly different kinetics. Whilst we ultimately show that the two processes are mechanistically related, vide infra, we discuss data for the two systems separately below, beginning with TBAT-initiation.[10]

3. TBAT mediated CF_2 Generation from $TMSCF_3$. The kinetics of reaction of **3i** with $TMSCF_3$ (**1**) initiated by TBAT in THF were analysed in detail by in situ ^{19}F NMR spectroscopy. The process afforded simple and reproducible temporal-concentration profiles, in which **1** and **3i** are consumed, and TMSF and **6i** are generated, Figure 1A. Although the decay in [**1**] correlates directly with the growth in [TMSF], the difluorocyclopropanation product [**6i**] does not. Competing side-reactions consume excess **1**, still generating TMSF, but not **6i**, vide infra, making the productive fractionation, $f = v_{6i}/v_{TMSF}$, a useful mechanistic parameter.

$$\textit{excess}\ TMSCF_3 + \mathbf{3i} \rightarrow \textit{excess}\ TMSF + \mathbf{6i} \qquad f = v_{6i}/v_{TMSF}$$

Figure 1. Examples of reaction of alkene **3i** (0.6 M) with **1** (1.5 M), mediated by TBAT (Graphs A, 18 mM) and by NaI (Graphs B, 32 mM), analyzed in situ by ^{19}F NMR spectroscopy.

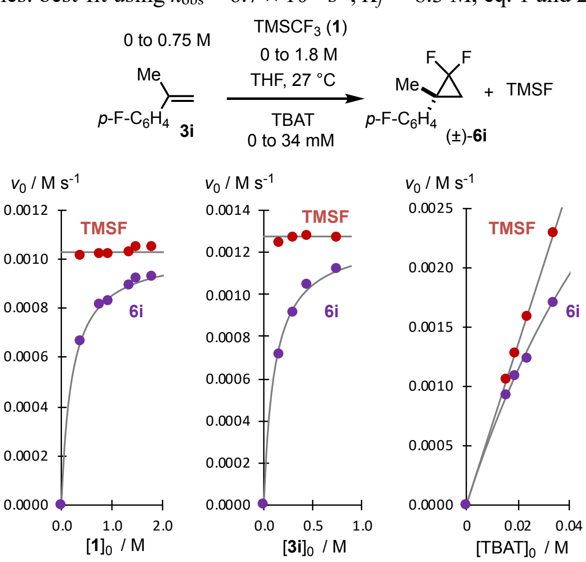


3.1 Empirical Rate Law and Fractionation, *f*. Systematic variation of the reactant concentrations led to empirical relationships (equations 1 and 2) for the *initial* rate (v_0) and fractionation (f_0) for conditions A, Figure 2.

$$v_0 = \frac{-d[\mathbf{1}]}{dt} = \frac{d[\mathrm{TMSF}]}{dt} \approx k_{obs}[\mathrm{TBAT}]_0 \qquad \text{(eqn. 1)}$$

$$\frac{d[\mathbf{6i}]}{dt} = \frac{f_0\, d[\mathrm{TMSF}]}{dt} \qquad f_0 \approx \frac{1}{1 + \left(\frac{K_f[[\mathrm{TBAT}]_0}{[\mathbf{1}]_0[\mathbf{3i}]_0}\right)} \qquad \text{(eqn. 2)}$$

Figure 2. Initial rates (v_0/M s^{-1}) of TMSF / **6i** generation in the TBAT-initiated reaction of **3i** with **1**.[a] Circles: experimental data. Lines: best-fit using $k_{obs} = 6.7 \times 10^{-2}$ s^{-1}, K_f = 8.3 M, eq. 1 and 2.

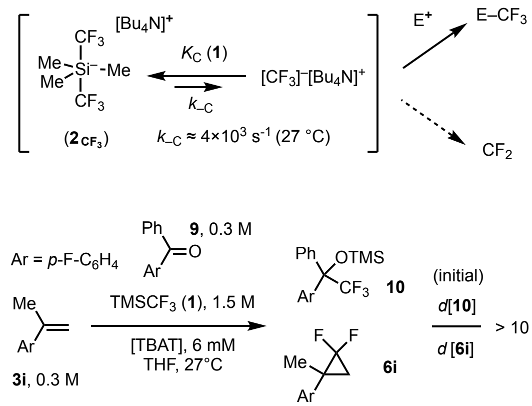


a. Conditions: THF, 27 °C. Unless stated, $[\mathbf{1}]_0$ = 1.5 M; $[\mathbf{3i}]_0$ = 0.6 M; $[\mathrm{TBAT}]_0$ = 0.018 M. Data by in situ ^{19}F NMR spectroscopic analysis. Values for $[\mathbf{1}]_0$ corrected for initial consumption of reagent by trace H_2O, as estimated from $[CF_3H]_0$.

The side reactions that reduce the productive fractionation, $f < 1$, also cause inhibition, vide infra, resulting in progressive deviation from the initially pseudo zero-order kinetics (eqn. 1).

3.2 Analysis of Siliconate $\mathbf{2_{CF3}}$. Variable temperature ^{19}F NMR spectroscopic analysis of the reaction of TBAT with a large excess of $TMSCF_3$ (**1**) and alkene (**3i**) confirms that the TBAT is immediately consumed, to quantitatively generate siliconate $\mathbf{2_{CF3}}$ (δ_F –63.0 pm),[18] plus TMSF (δ_F –157.1 pm), Ph_3SiF (δ_F –169.7 pm), and Ph_3SiCF_3 (δ_F –58.4 pm).[29] Under the conditions employed for the preliminary kinetic analyses at 300 K, Figure 2, the signal for $\mathbf{2_{CF3}}$ is not evident in the ^{19}F NMR spectrum due to extensive line-broadening caused by rapid, endergonic, equilibrium ($1/K_C$) with **1** and the corresponding CF_3-anionoid, Scheme 4.[16,17]

Scheme 4. Complexation (K_C) of CF_3-anionoid with **1** to generate siliconate $\mathbf{2_{CF3}}$, and competing CF_2 generation versus electrophilic capture of CF_3-anionoid. k_{-C} by SF-^{19}F-NMR[16] line-shape, see SI.



In the absence of an alkene, siliconate $\mathbf{2_{CF3}}$ is relatively unstable ($t_{0.5}$ ~1 min at 13 °C), decomposing to TMSF, plus a mixture of perfluorinated species, including TFE, $TMSCF_2CF_3$, CF_3H (see section 6), and complex anions, vide infra.[18] The rate of decomposition of $\mathbf{2_{CF3}}$ is substantially attenuated by the presence of alkene (**3i**) which captures the CF_2 (to generate **6i**).[30] Variable temperature stopped-flow ^{19}F NMR spectroscopy (VT-SF-^{19}F NMR)[16] allowed the siliconate $\mathbf{2_{CF3}}$, and the generation of TMSF, and transfer of CF_2, to be studied in detail between 2 and 22 °C, see section S1.9 in the SI. Simulation of the ^{19}F NMR line-width data of siliconate $\mathbf{2_{CF3}}$ indicates that CF_3-anionoid dissociation (k_{-C}, Scheme 4) is rapid ($\Delta G_{300}^{\ddagger}$ = 13 kcal mol^{-1}; $\Delta S^{\ddagger}$ = 23 cal K^{-1} mol^{-1}). In contrast, the *overall* rate of TMSF generation has a higher barrier ($\Delta G_{298}^{\ddagger}$ = 19 kcal mol^{-1}; $\Delta S^{\ddagger}$ = 18 cal K^{-1} mol^{-1}), consistent with the empirical rate law for cyclopropanation, $k_{obs} = 6.7 \times 10^{-2}$ s^{-1}, Figure 2.

Addition of competitive electrophilic species (E^+), that trap or divert the CF_3-anionoid,[16,17] inhibit or terminate CF_2-transfer from **1** to *p*-F-α-methylstyrene **3i**, see SI. For example, addition of CO_2 (13 mol%) results in generation of $[CF_3CO_2]^-$ and complete cessation of CF_2 generation. Analogously, hindered ketone **9** is converted to CF_3-addition product **10**, in advance of the difluorocyclopropanation product **6i** being generated; section S3.8G in the SI.

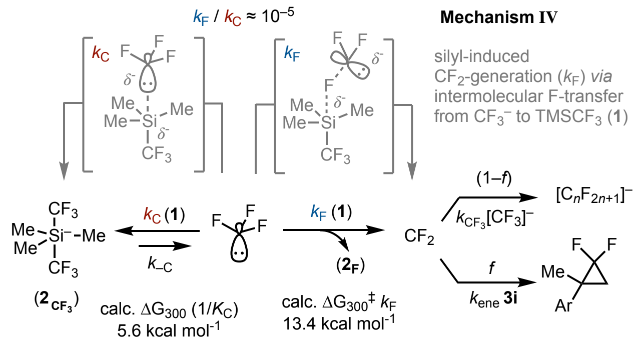
3.3 Mechanism of $\mathbf{CF_2}$-generation; TBAT. The experiments outlined above support the conclusion that CF_2 generation from **1** under conditions A (TBAT), involves the CF_3-anionoid / siliconate $\mathbf{2_{CF3}}$ equilibrium, Scheme 4. Prior mechanistic proposals have invoked *direct* α-elimination (k_α) from the CF_3-anionoid to yield CF_2 + F^-; in other words, a chain-reaction in which the CF_3-anionoid and F^- are the chain carriers (Mechanism I).[10,13b] However, as was analogously shown for the nucleophilic transfer of CF_3 from **1** to electrophiles,[16] exergonic complexation (K_C) of the CF_3-anionoid will result in the $TMSCF_3$ (**1**) acting as a powerful inhibitor in the kinetics of CF_2 generation (eqn. 3)*, which is not observed*: see equation 1, and left hand graph in Figure 2.

$$\text{(Mech I)} \quad \frac{d[\mathbf{6i}]}{dt} = f_0\, k_\alpha[\mathrm{CF_3}] \approx \frac{f_0\, k_\alpha\, [\mathrm{TBAT}]_0}{1 + K_\mathrm{C}[\mathbf{1}]} \quad \text{(eqn. 3)}$$

$$\text{(Mech IV)} \quad \frac{d[\mathbf{6i}]}{dt} = f_0\, k_\mathrm{F}[\mathrm{CF_3}][\mathbf{1}] \approx \frac{f_0\, k_\mathrm{F}[\mathrm{TBAT}]_0[\mathbf{1}]}{1 + K_\mathrm{C}[\mathbf{1}]} \quad \text{(eqn. 4)}$$

Moreover, DFT calculations indicate a prohibitively high barrier ($\Delta G_{300}^{\ddagger} \geq 27.6$ kcal mol^{-1}; $k_{obs} \leq 10^{-7}$ s^{-1}) for two-step liberation of CF_2, starting from the dominant anion, i.e. siliconate $\mathbf{2_{CF3}}$, and proceeding via α-elimination (k_α; Mechanism I). An analogous process in which the siliconate $\mathbf{2_{CF3}}$, rather than the CF_3-anionoid, undergoes α-elimination ($k_{\alpha Si}$; Mechanism III, Scheme 2) was also considered. Whilst the process would be consistent with the empirical rate-law (eqn. 1), DFT calculations in search of a TS for an *intramolecular* α-elimination at silicon in $\mathbf{2_{CF3}}$, ($k_{\alpha Si}$), failed. Instead the DFT optimizations diverted to a process in which silane **1** acts as an *intermolecular* acceptor of fluoride, from the CF_3-anionoid (k_F, Mechanism IV, Scheme 5). A low barrier is calculated for this elementary step ($\Delta G_{300}^{\ddagger} = 13.4$ kcal mol^{-1}). The predicted kinetics (eqn. 4; section S5.1 in the SI) are consistent with the empirical rate law (eqn. 1), when K_C is large. The *overall* barrier calculated for two-step CF_2-generation from $\mathbf{2_{CF3}}$, agrees well with experiment (k_F/K_C, $\Delta G_{300}^{\ddagger} = 19.1$ kcal mol^{-1}; $k_{obs} \approx 7 \times 10^{-2}$ s^{-1}).

Scheme 5. Mechanism IV: silyl-induced CF_2-generation (k_F). Energies (ΔG_{300} / kcal mol^{-1}) by DFT.[26]



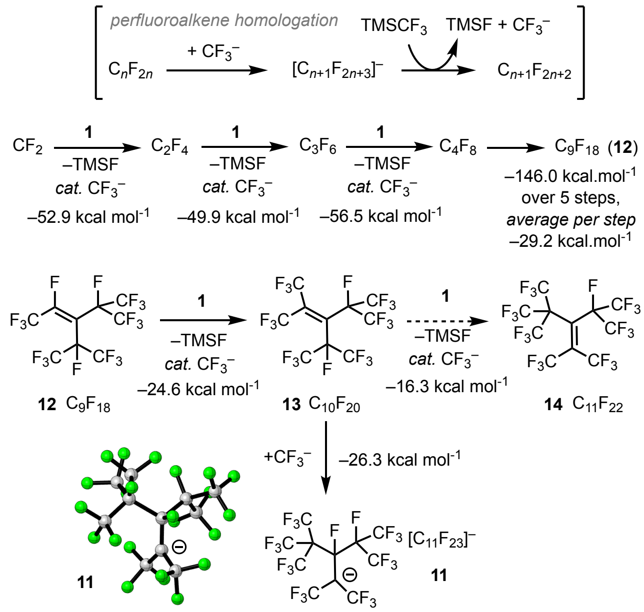
Equation 5 allows the CF_3-anionoid dissociation rate (k_{-C}, determined by VT-SF-^{19}F NMR, see section S1.9 in the SI) to be used to estimate the ratio of fluoride transfer to **1** (k_F) versus Si-complexation (k_C). Whilst the ratio doubles across the temperature range studied (2-22 °C), CF_2 is generated only once in every approximately 10^5 reactions of **1** with the CF_3-anionoid ($k_F/k_C = 1\pm0.4 \times 10^{-5}$). At 27 °C the k_F/k_C ratio corresponds to $\Delta\Delta G_{300}^{\ddagger} = 7$ kcal mol^{-1}, consistent with Si-complexation of the CF_3-anionoid (k_C) being close to diffusion-controlled. The low k_F/k_C ratio (10^{-5}) results in an excess of CF_3-anionoid being present during generation of CF_2, and thus competing side reactions (k_{CF_3}) which lead to $TMSCF_2CF_3$ and TFE, both of which accumulate in low concentrations (2-10 mM). Equation 6, see section S5.2 in the SI, incorporates the parameters that influence the efficiency of CF_2 capture by alkene, i.e. $k_{ene}[\mathbf{3i}]$, and the concentration of the CF_3-anionoid, i.e. K_C, $[\mathbf{2_{CF3}}]$ and $[\mathbf{1}]$, thus accounting for the empirical fractionation, f (eqn. 2, when $K_f \approx k_{CF3}/K_C\, k_{ene}$).[31]

$$\text{(Mech IV)} \quad \frac{d[\mathrm{TMSF}]}{dt} \approx \frac{k_\mathrm{F}}{k_\mathrm{C}}[\mathrm{TBAT}]_0\, k_{-\mathrm{C}} \quad \text{(eqn. 5)}$$

$$f \approx \frac{1}{\left(1 + \dfrac{k_{\mathrm{CF_3}}[\mathbf{2_{CF_3}}]_t}{K_\mathrm{C}[\mathbf{1}]_t \;\; k_{ene}[\mathbf{3i}]_t}\right)} \quad \text{(eqn. 6)}$$

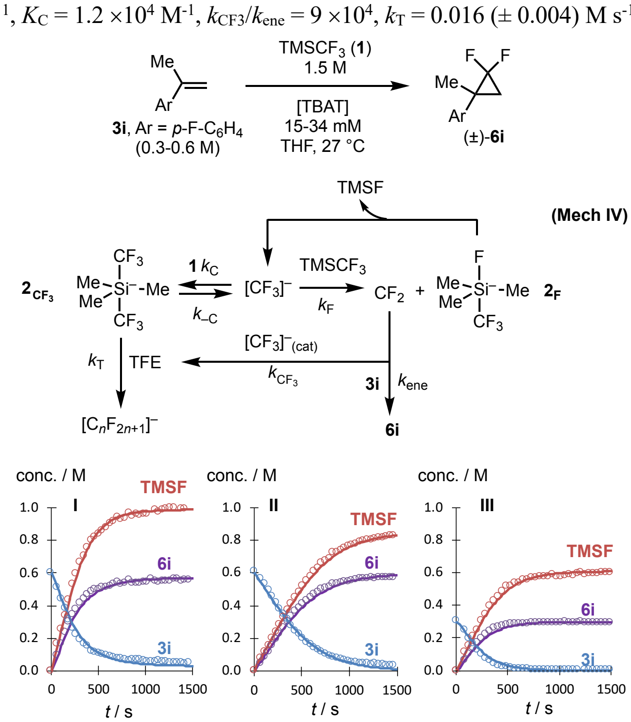
3.4 Chain-Termination: the $[C_{11}F_{23}]^-$ anion, 11. Difluorocyclopropanation under conditions A suffers progressive inhibition, with reactions sometimes stalling prior to complete consumption of alkene/yne, despite a large excess of $TMSCF_3$ (**1**). The lower the reactivity of the alkene/yne (k_{ene}), or the lower the initial concentration of **1**, the more rapid the onset of inhibition.

Scheme 6. Energies (ΔG_{300} / kcal mol^{-1}) calculated by DFT[26] for perfluoroalkene homologations see section S6.3 in the SI, leading to anion sequestration in **11**.[32,34] Values are discrete, not global.



In situ ^{19}F NMR spectroscopic studies and DFT calculations, see sections S1.8C and S6.3 in the SI, suggest the major decomposition product (~50%) of siliconate $\mathbf{2_{CF3}}$ is the tertiary perfluorocarbanion $[C_{11}F_{23}]^-$, **11**, Scheme 6.[32] This species accumulates during the difluorocyclopropanation of styrene **3i**, Fig. 1A, as the reaction becomes progressively inhibited. DFT calculations indicate that perfluoroalkene **12**,[33] a known trimer of perfluoropropene,[34a] and its homologue **13**, Scheme 6, are relatively free from steric strain. In contrast, **14** (and isomer) is highly strained, making fluoride elimination from **11**, $[C_{11}F_{23}]^-$, disfavored (ΔG_{300} +10.0 kcal mol^{-1}).

Figure 3. Selected simulations (see section S5.2 in the SI) using a simplified mechanism IV. **I**: TBAT 34 mM, $[\mathbf{3i}]_0$ 0.6 M; **II**: TBAT 15mM, $[\mathbf{3i}]_0$ 0.6 M; **III**: TBAT 18 mM, $[\mathbf{3i}]_0$ 0.3 M. $k_{-C} = 4 \times 10^3$ s^{-1}, $K_C = 1.2 \times 10^4$ M^{-1}, $k_{CF3}/k_{ene} = 9 \times 10^4$, $k_T = 0.016$ (± 0.004) M s^{-1}.



Thus, beginning with C_2F_4 (TFE), a series of CF_3-anion additions, 1,2-shifts, and then F^- eliminations via $TMSCF_3$,[34] see section S6.3 in the SI, results in the generation of a carbanion (**11**) that is sufficiently stabilized,[35] to terminate reaction involving **1**. Inclusion of a simplified pathway for chain-termination (k_T, TFE, Figure 3) in an anionic chain-reaction based on Mechanism IV, afforded a basic but functional model for the simulation (Figure 3) of the temporal evolution of the TBAT-initiated Prakash-Hu difluorocyclopropanation[10] of **3i**; conditions A.

4. NaI mediated CF_2 Generation from $TMSCF_3$. In contrast to TBAT, difluorocyclopropanation under conditions B (NaI)[10] effects complete conversion of alkenes *E/Z*-**4**, and alkyne **5** (see section S3.2 and S3.3 in the SI, and k_{rel}, Table 1), and proceeds without progressive inhibition. Exploration of the NaI-mediated reaction of **1** with **3i**, using a wide range of alternative activators, additives, and inhibitors, see section S1.10 in the SI, indicated that *both* the sodium and the iodide, are essential components for efficient reaction. For example, whilst an in situ combination of $[Hex_4N][I]$ (5.2 mol %) with $NaBAr_4$ (5 mol %), was as equally effective as NaI, neither component was effective in isolation, and addition of 15-crown-5 to the NaI-mediated reaction resulted in powerful inhibition. LiI and KI were much less effective than NaI, affording ≤ 10% difluorocyclopropane **6i**, over 2 days at 65 °C - conditions under which NaI effects 100 % conversion of **3i** to **6i** in minutes to hours.

Other nucleophilic / reducing species, M^+X^- (M = Bu_4N, Li, Na, K), including MOtBu, MOAr, MO_2CR, MOTMS, TEMPO-M, and M-naphthalenide, induced TMSF-generation from **1**, displaying a wide range of efficiencies for CF_2-transfer to **3i** (f = 0.01 to 0.95). However, most reactions underwent progressive inhibition, all generated TFE, and none displayed auto-acceleration, vide infra. Attempts to induce electrochemically-mediated TMSF + CF_2 generation from **1** were only moderately effective: reactions initially displayed high productive fractionation, but quickly stalled, with side products and decomposition of **6i**, evident, see section S1.10K in the SI.

4.1 In Situ ^{19}F NMR Analysis. Attempts to establish an empirical rate law for the NaI mediated reaction of **3i** with **1** were thwarted by large kinetic variations between and within runs, See Figure 1B, and sections S2.2DE in the SI. All of the reactions studied underwent one or more short periods of acute auto-acceleration[36] with the rate of TMSF generation increasing by a factor 10^2-10^3 ($v_{max} \approx 2 \times 10^{-2}[\mathbf{1}]_t$ Ms^{-1}). Whilst the occurrence and duration of these periods varied substantially between runs, in general the lower the initial concentration, or reactivity (k_{ene}, Table 1), of the alkene/yne, the earlier the onset of auto-acceleration, see section S3.8 in the SI.

Preceding auto-acceleration is a phase of slow generation of **6i** + TMSF with very high efficiency ($f \geq 0.99$ under all conditions examined) and no evident correlation of the rate ($3\pm2 \times 10^{-5}$ M s^{-1}) with $[NaI]_0$, $[\mathbf{3i}]_t$, or $[\mathbf{1}]_t$. During the final auto-acceleration, the productive fractionation is substantially reduced ($f \leq 0.1$; see sections S2.2CD in the SI), initially through generation of TFE, to a maximum concentration of 0.25±0.1 M, before being depleted by conversion to perfluorocyclopropane (c-C_3F_6),[12i] and a plethora of other minor species, including CF_3I and further CF_3H.

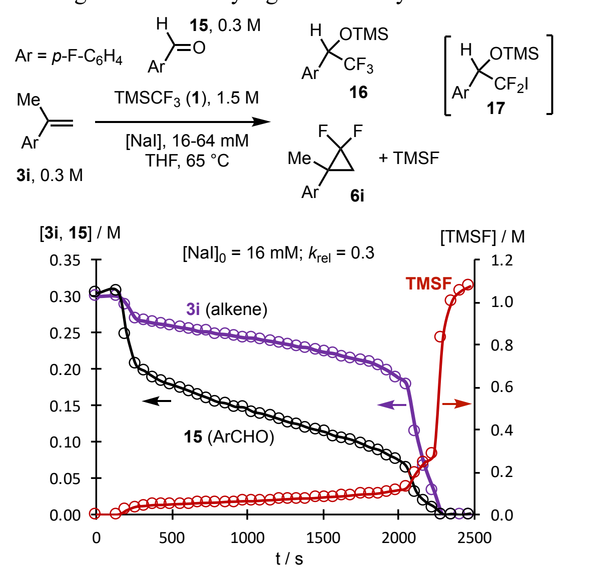
In situ ^{19}F NMR spectroscopy during the periods of auto-acceleration suggests that the process causes chemical or physicochemical inhomogeneity within the NMR sample,[36] resulting in broad and asymmetric ^{19}F NMR signals in all of the reaction components, including the internal standard, section S2.5B in the SI. This line-broadening hinders identification of transient species generated during acute periods of auto-acceleration. As auto-acceleration attenuates, the ^{19}F NMR signals return to normal (sharp, symmetric).[36] Prior to auto-acceleration, the only species detected by in situ ^{19}F NMR spectroscopy (> 0.05 mol%; as referenced against ^{13}C-satellites) apart from **1**, TMSF, alkene **3i**, product **6i**, and the internal standard (PhF), were traces of CF_3H (see section 6).

4.2 Intermediacy of $NaCF_3$. A variety of electrophilic additives, e.g CO_2, which again generated $[CF_3CO_2]^-$, inhibited difluorocyclopropanation, section S2.3 in the SI. However, in contrast to the TBAT-initiated process, Scheme 4, co-reaction of alkene **3i** and ketone **9** resulted in difluorocyclopropanation without any significant CF_3-transfer to **9**, indicative of a much lower concentration of CF_3-anionoid. With the more reactive aldehyde **15**, the CF_3-addition product **16** is co-generated, Figure 4.

Analysis of $[\mathbf{3i}]_t/[\mathbf{15}]_t$ as a function of net conversion, revealed that throughout reaction, i.e. before, during, and after auto-acceleration, the two processes {**3i** + CF_2; Scheme 3}, and {**15** + $NaCF_3$}[17] *are competitive and synchronized*. Moreover, the relative reactivity of **3i** to **15** (k_{rel}) is found to vary in proportion to the [NaI] concentration, see section S3.8I in the SI, with higher concentrations of NaI increasing the relative-rate of consumption of **3i** over **15**. The first-order dependency of this partitioning on all three components (i.e. **3i**, **15** and NaI) is indicative that the two competing reactive intermediates, CF_2 and $NaCF_3$, *are in equilibrium*, with NaI biasing this equilibrium in favor of the CF_2, see section S5.3 in the SI, and equation 7, $K_{rel} \approx 1.7 \times 10^1$ M^{-1}.

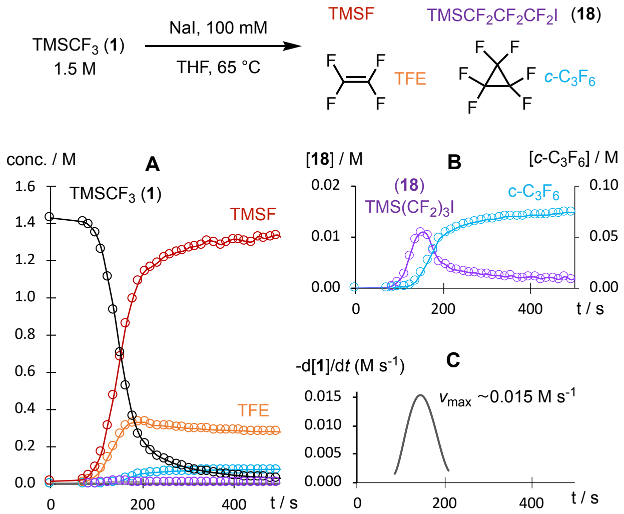
$$\frac{-d[\mathbf{3i}]/dt}{-d[\mathbf{15}]/dt} = \frac{k_{ene}\,[\mathbf{3i}]\,[CF_2]}{k_{ald}\,[\mathbf{15}]\,[NaCF_3]} = k_{rel}\,\frac{[\mathbf{3i}]}{[\mathbf{15}]} \qquad k_{rel} \approx K_{rel}\,[NaI] \qquad \text{(eqn. 7)}$$

Figure 4. Difluorocyclopropanation of **3i** versus CF_3-addition to **15**, mediated by NaI, analyzed by in situ ^{19}F NMR spectroscopy. The CF_2I-addition product **17** is only detected in the absence of **3i**. Lines through data are solely a guide to the eye.



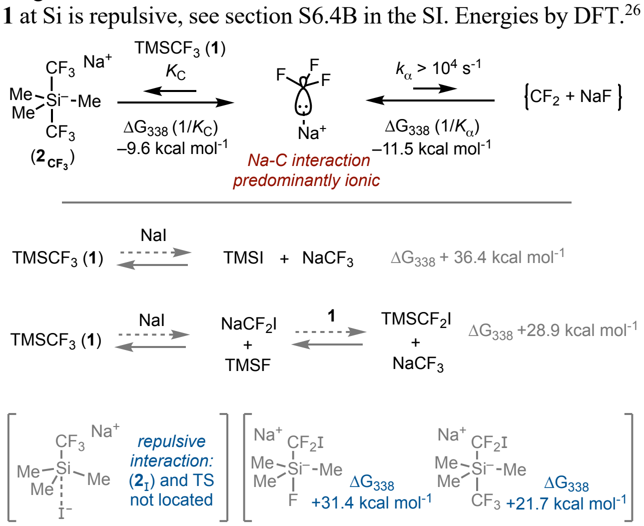
In the absence of alkene **3i**, traces of the CF_2I-addition[9h] product **17** (0.9 %) were also generated,[37] and reactions conducted in the absence of both **3i** and **15** rapidly underwent auto-acceleration, again generating TFE (0.25±0.1 M), and white precipitates containing NaF. Detailed in situ analyses of this process, see Figure 5 and section S2.5 in the SI, revealed that low concentrations of a transient species, tentatively identified as $TMSCF_2CF_2CF_2I$, **18**,[38] are generated immediately after TFE begins to appear. The concentration of **18** (Figure 5B) correlates with the degree of auto-acceleration, reaching a maximum concentration at the point of maximum rate of $TMSCF_3$ **1** consumption (Figure 5C). The decay in TFE, and **18**, correlate with the growth of c-C_3F_6.

Figure 5. Auto-accelerating decomposition of $TMSCF_3$ (**1**) mediated by NaI in THF at 65 °C, in the absence of exogenous alkene. Analysis by in situ ^{19}F NMR spectroscopy. Lines through data are solely a guide to the eye. -d[**1**]/d*t*: was estimated from the first-derivative of truncated polynomial fitted between 85-210 s.



4.3. Mechanism of CF_2 generation; NaI. The above analysis (section 4.2) supports the intermediacy of a CF_3-anionoid in an anionic chain reaction that generates CF_2 from $TMSCF_3$ (**1**), as has previously been suggested.[10,13b,f] However, unlike TBAT initiation, $TMSCF_3$ is not predicted to inhibit the chain reaction by siliconate $\mathbf{2_{CF3}}$ generation (calc. $K_C \leq 10^{-5}$; Scheme 7), due to a stronger, but still predominantly ionic, interaction of Na^+ with the CF_3 anionoid; see section S6.4B in the SI. Moreover, the interaction of the CF_3 anionoid with Na^+ raises the barrier of silyl-induced elimination via F^- anion transfer (compare k_F, mechanism IV, Scheme 5) to $\Delta G_{338}^{\ddagger}$ = +21.4 kcal mol^{-1}; substantially above the barrier for direct α-elimination, k_α, Scheme 7. Indeed, on first-inspection, if the reaction proceeds via an α-elimination pathway ($NaCF_3 \rightarrow CF_2 + NaF$, calc. $k_\alpha \sim 10^4$ s^{-1}), *just micromolar concentrations*[39] of $NaCF_3$ are required to sustain the fastest rates of TMSF-generation observed ($v_{max} \approx 2 \times 10^{-2}$[**1**]; see section S2.5B in the SI).[39]

Scheme 7. Upper section: disfavored Si-complexation (K_C) of $NaCF_3$, and rapid, reversible α-elimination (k_α). Lower: Highly endergonic routes to $NaCF_3$ from NaI and **1**. Interaction of NaI with **1** at Si is repulsive, see section S6.4B in the SI. Energies by DFT.[26]

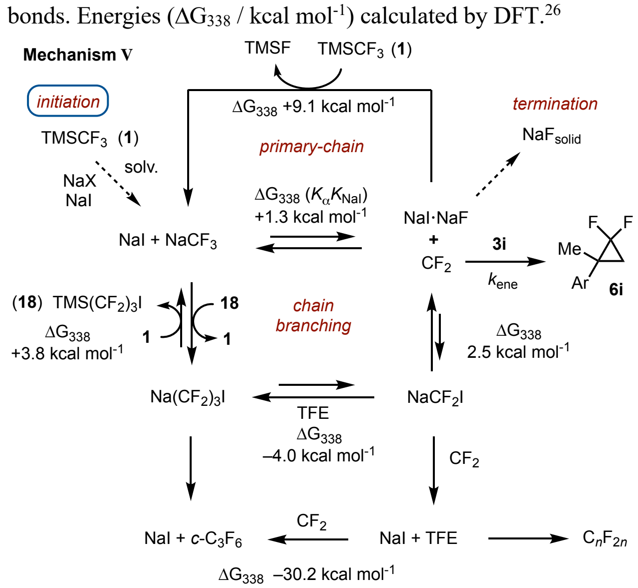


However, initiation of the anionic chain by *direct* reaction of **1** with NaI to generate $NaCF_3$ (Mechanism II)[10,13b,f] is calculated to be strongly disfavored, Scheme 7. Indeed, exogenous TMSI and $TMSCF_2I$ are both powerful inhibitors of the NaI-mediated reaction of **1** with **3i**, see sections S2.3EJ in the SI. In addition, no TMSI, or THF ring-opened co-products,[41] are detected by in situ ^{29}Si and ^{1}H NMR spectroscopy. Moreover, there is no direct correlation between $[NaI]_0$ and rate, or an induction period after addition of the NaI.

Initiation must therefore be effected by traces of unidentified silaphilic species generated in situ from the NaI, by oxidation,[42] reaction with decomposition products of the $TMSCF_3$,[16] co-reaction with the Lewis basic THF solvent, or already present in the NaI from manufacture.[43] Traces of white flocculate are observed in the reactions of **1** mediated by NaI (3.5 mol%), in the presence and absence of alkene **3i**. The precipitates become much more voluminous in the final phases of reaction. Analysis of the precipitate (^{19}F NMR in D_2O) obtained after 12-16 % conversion of **3i**, showed it contains NaF (0.005-0.02 mol%); see section S2.2D in the SI. After full auto-acceleration, 1.9 mol % NaF had been precipitated. However, the reactions of **1** with **3i** are not initiated by powdered NaF, or accelerated by exogenous NaF in the presence of NaI, see section S1.10I in the SI. In other words, microcrystalline NaF is insoluble and inert under the reaction conditions. Despite extensive efforts, we have not yet been able to identify the primary initiation route(s).

Thus, the primary role of the NaI appears to be to *mediate* efficient difluorocyclopropanation, vide infra, via an anionic chain reaction proceeding at very low concentrations of chain-carrier.[39] Our analysis of the role of NaI in mediating the desired difluorocyclopropanation thus centres on the α-elimination step (k_α, upper section of Scheme 7). Although calculations show this process to be rapid, it is also endergonic, see section S6.4B in the SI, with CF_2 + NaF (monomeric) reverting to $NaCF_3$ at diffusion-control.[39] However, the equilibrium concentration of CF_2 can be raised by coupling the endergonic α-elimination (K_α) to an exergonic complexation with NaI[44] (K_{NaI}), see Scheme 8.

Scheme 8. Mechanism V: NaI-mediated chain-reaction for the generation of CF_2 from $TMSCF_3$ (**1**) with auto-acceleration via chain-branching. NaF_{solid} precipitation increases substantially during auto-acceleration. Primary initiation is by trace unidentified silaphilic species (see text). Additional chain-branching processes are also possible. Na-intermediates are primarily bound through ion-pair interactions, see section S6.4B in the SI, not covalent bonds. Energies (ΔG_{338} / kcal mol^{-1}) calculated by DFT.[26]

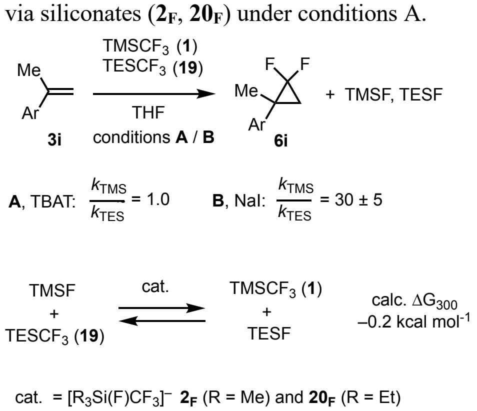


Analogous dinuclear NaX·NaX complexes (X = F, Cl, Br, I) have been characterized in the gas phase,[44b] and related synergistic alkali-metal effects are known.[45] Whilst the stoichiometry of complexation (K_{NaI}, to generate $NaF{\cdot}(NaI)_x$) has not been evaluated directly, the first-order correlation of [NaI] with k_{rel} (equation 7) in the competition of alkene **3i** with aldehyde **15**, Figure 4, suggests that x is close to unity. Chain propagation, by direct or dissociative reaction of NaF·NaI with **1**, regenerates transient $NaCF_3$ in micromolar concentrations, Scheme 8, allowing efficient difluorocyclopropanation of the alkene/yne ($f \geq 0.99$). NaI thus serves at least three roles: i) it indirectly generates chain-carrier, ii) it biases the endergonic equilibrium with CF_2, i.e. ($K_\alpha K_{NaI}$), and in doing so attenuates the undesired reaction of CF_2 with $NaCF_3$, and iii) it stabilizes the NaF chain-carrier by inhibiting generation of NaF_{solid}.

4.4. Chain-Branching; Auto-acceleration by NaI. In competition with CF_2-capture by the alkene (k_{ene}) is the mildly endergonic (ΔG_{338} = 2.5 kcal mol^{-1}) reversible addition of NaI to CF_2 to generate $NaCF_2I$,[9h] resulting in generation of **17**, when an aldehyde is present, Figure 4. Although silylation of $NaCF_2I$ is disfavored ($NaCF_2I$ + **1** $\rightarrow$ $NaCF_3$ + $TMSCF_2I$, ΔG_{338} = 16.0 kcal mol^{-1}) primarily because of the steric clash between iodine and the TMS in the resulting $TMSCF_2I$,[9h] reaction of $NaCF_2I$ with CF_2 will generate TFE (ΔG_{338} = –59.5 kcal mol^{-1}); in other words, NaI can catalyze the dimerization of CF_2.[46] Subsequent exergonic reaction of the TFE with $NaCF_2I$ (or with NaI, followed by CF_2), will generate $I(CF_2)_3Na$. This can either cyclize, generating c-C_3F_6, or be *reversibly* silylated by **1** to generate **18** and $NaCF_3$. The latter process facilitates indirect chain-branching, i.e. increases [$NaCF_3$], thus accelerating the chain reaction, and facilitating competing side reactions such as capture of CF_2 by $NaCF_3$ to generate further TFE and NaF. A number of processes will attenuate branching, or the chain reaction itself, including the reverse reaction of $NaCF_3$ with **18** to regenerate **1** + $I(CF_2)_3Na$ (and c-C_3F_6), CF_2-capture by alkene, CF_2-capture by TFE to generate c-C_3F_6,[12i] aggregation of $(NaF)_n$ leading to precipitation of inert, microcrystalline, NaF_{solid}, and trapping or oxidation of $NaCF_3$ by perfluoroalkenes, vide infra, generated from TFE. A characteristic of branched chain-reactions is their sensitivity to small changes in the concentrations of components, heterogeneity, and trace inhibitors, in some cases leading to fluctuations in active species and irreproducible kinetics,[47] as is observed in the current system,[36] Figure 1B, see also sections S2.2D and S2.5B in the SI.

5. $TESCF_3$ versus $TMSCF_3$. Reactions involving the more sterically hindered reagent $TESCF_3$ (**19**) were briefly explored, see section S3.9 in the SI. Under TBAT-initiation, in the presence of alkene **3i**, mixtures of $TESCF_3$ (**19**) and $TMSCF_3$ (**1**) co-evolved TMSF, TESF, and product **6i**, with very little apparent selectivity for reaction of **1** over **19**. This initially confusing result is different to our previous studies of TBAT-initiated CF_3-transfer to ketones and aldehydes,[16] where $TMSCF_3$ (**1**) reacted in advance of $TESCF_3$ (**19**). The result can be understood by the intermediacy of fluorosiliconates ($\mathbf{2_F}$/ $\mathbf{20_F}$) in mechanism IV, which allow equilibration of TMSF/$TESCF_3$ with $TMSCF_3$/TESF, calc. ΔG_{300} –0.2 kcal mol^{-1}, Scheme 9.

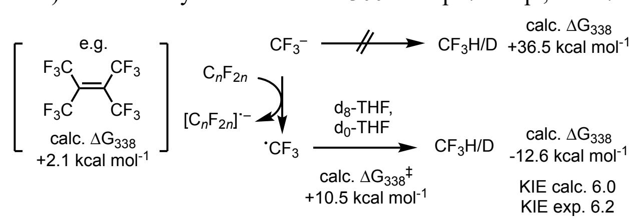
Scheme 9. Differing outcomes of co-reaction of $TESCF_3$ (**19**) and $TMSCF_3$ (**1**) under conditions A (TBAT) versus B (NaI), with equilibration via siliconates ($\mathbf{2_F}$, $\mathbf{20_F}$) under conditions A.



In contrast, co-reactions of $TESCF_3$ (**19**) and $TMSCF_3$ (**1**) mediated by NaI, proceeded selectively (k_{TMS} / k_{TES} ~ 30, see S3.9BC in the SI) in both the presence and absence of alkene **3i**. This is consistent with siliconates (**2**, **20**) being disfavored in the presence of Na^+, allowing the selective reaction of the more fluorophilic reagent **1**.

6. Fluoroform (CF_3H) Generation. There have been conflicting reports in the literature about whether a CF_3 anionoid is able to deprotonate THF to generate CF_3H.[17a,c] In all of the reactions explored herein, CF_3H was detected, see e.g. Fig 1. However, CF_3H is generated in two distinct phases. Under the standard conditions, Table 1, approximately 0.4 mol% CF_3H is generated immediately after the reaction is assembled. This arises from protonation of the CF_3 anionoid[16,17] by residual H_2O (20 ppm, KF-titration) in the THF, as confirmed by ^2H labelling. Further CF_3H (up to 18 mM, 1-1.2 % of **1**) is generated in the later stages of the reaction, either progressively (TBAT) or in a final 'burst' (NaI, see Figure 1B). The source of H-atom in this distinct second stage of CF_3H generation is the THF, as confirmed by ^2H labelling, section S2.4A in the SI. Calculations indicate that deprotonation of THF by the CF_3 anionoid is highly endergonic. However, abstraction of an H-atom by a CF_3 radical[48] is favorable,[49] and the calculated KIEs are consistent with those determined experimentally, Scheme 10, see sections S2.4B and S6.7 in the SI.[49g]

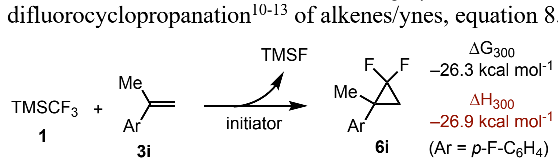
Scheme 10. CF_3H generation from THF; C_nF_{2n} = higher perfluoroalkene, e.g. 2,3-$(CF_3)_2C_4F_6$, as indicated. Energies (ΔG_{338} / kcal mol^{-1}) calculated by DFT.[26] KIEs at 300 K: exp. 7.2 exp., calc. 7.4.



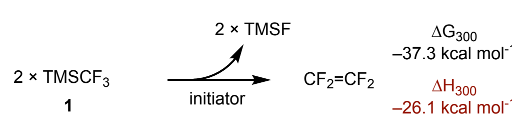
Computational exploration of single-electron-transfer to perfluoroalkenes, see SI, indicates that higher C_nF_{2n} species, e.g. Scheme 6, can readily generate a CF_3 radical[48,49] from the CF_3 anionoid, thus accounting for the differing phases of CF_3H evolution under conditions A, and B. In contrast to THF, reactions conducted in MeCN develop CF_3H throughout their evolution, and comparison of experimental and calculated KIEs with two alternative tunnelling approximations, see SI, indicate that this is via deprotonation.[50]

CONCLUSIONS

We have investigated the mechanism by which the commercially-available reagent $TMCF_3$ (**1**), widely-applied for CF_3-transfer,[16-18] can also function as source of CF_2.[10-13] Despite co-generation of TMSF, and thus a strong Si-F bond, the liberation of CF_2 from $TMSCF_3$ is endergonic (ΔG_{300} + 11.8 kcal mol^{-1}; 1M standard state in THF). However, by coupling this to a process that captures the CF_2, a thermodynamically-favorable, and usually exothermic, reaction can be established. Thus, in the presence of a suitable initiator / mediator, $TMSCF_3$ can be a highly-effective reagent for difluorocyclopropanation[10-13] of alkenes/ynes, equation 8.



(eqn. 8)



(eqn. 9)

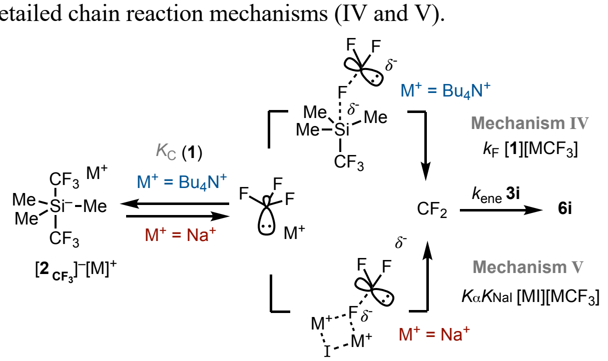
Two general sets of conditions have been described for this: TBAT-initiation (conditions A) and NaI-initiation (conditions B), in THF,[10-13] Scheme 1. Both require an excess of $TMSCF_3$ (**1**) over the alkene/yne CF_2-acceptor.[10,11c,12] The NaI-mediated method has also been widely applied for CF_2-transfer to a range of other species, and also for the in situ generation of TFE, equation 9.[13]

Analysis of $^{13}C/^{2}H$ KIEs, LFERs, and alkene competition experiments, confirms that both sets of conditions (A and B) liberate free, transient, singlet CF_2 (Scheme 3). The transient intermediate CF_2 adds to most alkenes and alkynes via a concerted cycloaddition transition state, Scheme 3. 1-Phenylpropyne is more reactive[51] than beta-methyl styrene towards CF_2, Table 1. Trans beta-methyl styrene is more reactive than its cis isomer, due to destabilizing steric interactions between cis-substituents that are enhanced on approach to the state; see section S6.2 in the SI for further discussion.

The mechanisms by which carbene CF_2 is generated from $TMSCF_3$ (**1**) have been investigated in detail using in situ / stopped-flow ^{19}F NMR spectroscopy, kinetics and simulation of the difluorocyclopropanation of α-methylstyrene **3i**, analysis of CF_2-transfer efficiency, the effect of inhibitors, and density functional theory (DFT) calculations. Having eliminated a wide range of mechanistic possibilities, including radical chain reactions, cationic chain reactions, and direct anion-induced liberation of CF_2 from $TMSCF_3$, see sections S1.4, S2.3 and S6.8 in the SI, we conclude that both sets of conditions proceed via anionic chain reactions, in which a CF_3-anionoid is a key intermediate, albeit present at very much lower concentrations under the NaI-mediated conditions.

Both processes require a fluoride-acceptor to enable efficient generation of highly-reactive CF_2 from the CF_3-anionoid, Scheme 11. When loosely ion-paired, e.g. with Bu_4N^+, the CF_3-anionoid undergoes silyl-induced fluoride elimination by $TMSCF_3$ **1** (k_F; Mechanism IV, Scheme 5). With the more closely associated cation, Na^+, an NaI-assisted α-elimination ($K_\alpha K_{NaI}$; Mechanism V, Scheme 8) predominates. Key to efficient alkene/yne difluorocyclopropanation is minimizing the competing reaction of the CF_3-anionoid with the CF_2.

Scheme 11. Pathways to CF_2 from CF_3-anionoids, generated in situ in anionic chain reactions involving $TMSCF_3$ (**1**) where M+ = Bu_4N^+ (TBAT initiation), or Na^+ (NaI-mediation). Autoinhibition and auto-acceleration not shown; see Schemes 5 and 8 for more detailed chain reaction mechanisms (IV and V).



The TBAT-initiated process ($M^+ = Bu_4N^+$) proceeds with very reproducible kinetics, but undergoes progressive inhibition via perfluoroalkene homologation, see Scheme 6 and section S6.3 in the SI, eventually leading to $[C_{11}F_{23}]^-$, **11**, and analogous species that are inert for F-anion transfer to **1**. Higher concentrations of **1** increase the efficiency of CF_2-transfer, *f*, equation 6, by reducing the concentration (via K_C) of the CF_3-anionoid that leads to non-productive consumption of **1**. The TBAT procedure is only suitable for alkenes/ynes that have sufficient reactivity (k_{ene}) towards singlet CF_2 to compete with the CF_3-anionoid and avoid extensive inhibition.

In contrast to TBAT, the NaI-mediated process displays non-reproducible kinetics, see Figs. 1B and 5, and sections S2.2D and S2.5 in the SI, indicative of fluctuations in low concentrations of active species, with variable delays before one or more acute auto-accelerations, via chain branching, Scheme 8. Under nearly all conditions this leads to rapid and near-complete consumption of the $TMSCF_3$ (**1**), and co-generation of TFE. Counterintuitively, less reactive alkenes/ynes (k_{ene}, Scheme 8, k_{rel}, Table 1), can (phenomenologically) undergo more rapid difluorocyclopropanation by **1** / NaI, due to the earlier onset of auto-acceleration, provided that the alkene/yne is sufficiently more-reactive towards CF_2 (k_{ene}) than the accumulating TFE ($\Delta G_{338}^{\ddagger} = 12.2$ kcal mol^{-1}). These counteracting effects, may account for the apparently anomalous alkene reactivities noted in previous studies.[12m] In the case of alkyne **5**, the barrier to the first CF_2 addition to generate **8** ($\Delta G_{338}^{\ddagger} = 12.0$ kcal mol^{-1}) is lower than for TFE, whilst that for second addition ($\Delta G_{338}^{\ddagger} = 17.4$ kcal mol^{-1}) is higher. The overall result is that double-addition[11] of CF_2 is avoided, i.e. the difluorocyclopropene **8** (Table 1) is selectively generated, see section S3.3 in the SI

In all cases, the productive fractionation (*f*) of $TMSCF_3$ into the difluorocyclopropanation product, is substantially attenuated during NaI-mediated auto-acceleration, and an excess of **1** is still required. As shown by Grygorenko and co-workers,[12m,] the slow addition of a large excess of **1** (up to 10 equiv.) can be used to achieve good conversion of a range of electron-deficient alkenes. Slow-addition can increase the productive fractionation, *f*, by curtailing, or attenuating, auto-acceleration, and allowing TFE to dissipate or decay. For example, sequential additions of $TMSCF_3$ (**1**) to methyl acrylate results in a series of auto-accelerations, and TFE accumulation / partial depletions, with somewhat improved levels of difluorocyclopropanation as compared to addition of **1** in a single portion, see section S3.4 in the SI.

Finally, we note two important practical aspects relating to the CF_2-generating reactions investigated herein. Firstly, the conditions always co-generate a range of perfluoroalkenes, e.g. Scheme 6, *many of which are volatile and toxic.*[52] Secondly, the kinetics of reactions mediated by NaI can undergo acute and unpredictable auto-acceleration, e.g. Figure 1B, resulting in *rapid generation of TMSF (b.p 19 °C),*[53] *and highly-exothermic capture of CF_2*; equations 8 and 9. Appropriate caution[12m,p] should be exercised in any reactions that generate transient singlet CF_2 from $TMSCF_3$ (**1**), or analogous reagents, *especially on scale-up*.[54] In this regard, the application of continuous flow technology may be advantageous,[12b] as may additives that can trigger and/or control auto-acceleration.

ASSOCIATED CONTENT

Supporting Information: Additional discussion, experimental procedures, further kinetic data and analysis, characterization data and NMR spectra, and full computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(28) Although there was no detectable product (**6i**) on heating **1** with **3i** in THF (67 °C, 72 h.) in the absence of exogenous initiator, traces of TMSF, CF_3H, and other unidentified species are generated, see SI. The transition state barrier for gas-phase unimolecular elimination of CF_2 from F_3SiCF_3 (see ref. 21a) is estimated to be 27 kcal mol^{-1} (DFT calc. 23.0 kcal mol^{-1}). A substantially higher barrier (37.9 kcal mol^{-1}, 300 K) is calculated for $TMSCF_3$ (**1**), indicative of a half-life of >3 months at 140 °C.

(29) Ph_3SiF also undergoes reversible conversion to Ph_3SiCF_3; $[Ph_3SiX]_{tot}$, corresponds to $[TBAT]_0$.

(30) Tests based on the initial stoichiometry-ratio of **3i** / $TMSCF_3$ (**1**) are consistent with this: reactions run to exhaustion of alkene **3i**, with excess 1, did not re-initiate on addition of further **3i**. In contrast, reactions run to exhaustion of $TMSCF_3$ (**1**), with excess alkene **3i**, re-initiated on addition of further **1**.

(31) The analysis suggests that maintaining low concentrations of siliconate $\mathbf{2_{CF3}}$ will increase the productive fractionation, *f*, and attenuate auto-inhibition (k_{CF3}). This was tested by syringe-pump addition of a TBAT solution (total 2.6 mol%) to a mixture of $TMSCF_3$ (**1**; 1.5 M) + styrene *E*-**4** (0.7 M) in THF over a period of 10 hours at 21 °C. The conversion of *E*-**4** to *trans*-**7** increased from 23% to 62% compared to addition of TBAT in a single portion.

(32) a) The ^{19}F NMR signals for **11** are identical to those previously assigned to an isomeric structure (see ref. 32b), which we found failed to optimize in DFT calculations, and to be less consistent with the ^{19}F NMR data, see SI. (b) Tyrra, W.; Kremlev,M. M.; Naumann, D.; Scherer, H.; Schmidt, H.; Hoge, B.; Pantenburg, I. Yagupolskii, Y L. How Trimethyl(trifluoromethyl)silane Reacts with Itself in the Presence of Naked Fluoride—A One-Pot Synthesis of Bis([15]crown-5)cesium 1,1,1,3,5,5,5-Heptafluoro-2,4-bis(trifluoromethyl)pentenide. *Chem. Eur. J.* **2005**, *11*, 6514–6518.

(33) In CsF-initiated oligomerization of TFE in various glymes, pentamers, i.e. $C_{10}F_{20}$, were found to dominate the product distributions - see Graham, D. P.; Fluoride Ion Initiated Reactions of Perfluoro alpha-Olefins. I. Reaction of the Pentafluoroethyl Carbanion with Tetrafluoroethylene. *J. Org. Chem*. **1966**, *31*, 955-957.

(34) For perfluorocarbanion and perfluoroalkene oligimerizations, equilibrations and stabilities see ref. 26(o), and (a) Bayliff, A. E., Bryce, M. R.; Chambers, R. D.; Matthews, R. S. Direct Observation of Simple Fluorinated Carbanions. *J. Chem. Soc. Chem. Commun*. **1985**, 1018–1019; (b) Smart, B. E.; Middleton, W. J.; Farnham, W. B. Stable Perfluoroalkyl Carbanion Salts. *J. Am. Chem. Soc.* **1986**, *108*, 4905–4907 (c) Farnham, W. B. Fluorinated Carbanions. *Chem.Rev*. **1996**, *96*, 1633–1640.

(35) As noted by Smart and Farnham, ref. 34c, tertiary perfluorocarbanion stability is counter-cation dependent, and "controlled by a rather delicate balance of steric and electronic factors."

(36) Reactions were monitored using an NMR spectrometer fitted with a cryoprobe; these are known to be sensitive to changes in the ionic strength of analytes: Kelly, A. E.; Ou, H. D.; Withers, R.; Dotsch, V. Low-Conductivity Buffers for High-Sensitivity NMR Measurements. *J. Am. Chem. Soc.* **2002**, *124*,12013–12019. Precipitation becomes more extensive during auto-acceleration and may be the cause of, or augment, the line-broadening.

(37) Reactions conducted in MeCN gave greater proportions of CF_3-anionoid and CF_2I-anionoid addition products, see SI.

(38) Iodo-addition product **18** is a transient species, and was only detected in some runs, notably when the initial NaI concentration was high, and the alkene concentration low or zero. Other iodo-adducts may also be generated through other pathways to facilitate conversion of NaI into $NaCF_3$ and thus effect auto-acceleration.

(39) Calculations (see section S.6.4B in the SI) suggest $NaCF_3 \rightarrow CF_2 + NaF$ is barrierless, but endergonic ($\Delta G_{338} = 11.5$ kcal mol^{-1}); thus the rate of reversible elimination is estimated to be $k_\alpha \sim 10^4$ to 10^6 s^{-1}, based on an additional 2.5±1 kcal mol^{-1} for solvent reorganization. To sustain supply of CF_2 at sufficient rate to correlate with the maximum rates observed, ($v_{max} \approx 2 \times 10^{-2}$ [**1**] Ms^{-1}), would require $[NaCF_3] \sim 2$ µM when $k_\alpha \approx 10^4$.

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GRAPHICAL ABSTRACT